

Embargoed for Release:

3 p.m. ET, April 9, 2013

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In Washington, D.C.,

April 6-10, 2013:

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Engineered Antibody Demonstrated Safety, Efficacy in Wide Range of Advanced Tumors

- The PD-L1 antibody MPDL3280A displayed antitumor activity across a range of cancer types, including lung, kidney, colon and stomach cancers.
- MPDL3280A was well tolerated.
- Phase I study results demonstrated no limiting toxicities.

WASHINGTON, D.C. — The engineered antibody MPDL3280A, which targets a protein called programmed death-ligand 1 (PD-L1), was safe and effective for several cancers, according to phase I study results presented at the AACR Annual Meeting 2013, held in Washington, D.C., April 6-10.

“Our PD-L1 antibody was well tolerated, and there were no limiting toxicities,” said Michael S. Gordon, M.D., research director at Pinnacle Oncology Hematology in Scottsdale, Ariz. “It was active with antitumor activity across a broad range of cancers, and we have developed biomarker tools that we are testing, which may allow us to optimize patient selection for this novel therapy.”

PD-L1, a protein found on the surface of many cancer cells, impairs the immune system’s ability to fight cancer, according to Gordon.

“PD-L1 is essentially a plug, which inserts into an outlet (PD-1) on the surface of the immune T cells,” Gordon said. “As the T cells come close to the tumor, for example, they are engaged by PD-L1, which inserts into the outlet on the surface of the T cell. That starts a signal inside the T cell that blocks the T cell’s ability to kill the cancer cell.”

MPDL3280A, a human monoclonal antibody under development by Genentech, a member of the Roche Group, binds to PD-L1 and blocks this action.

Gordon and colleagues administered an escalating intravenous dose of MPDL3280A once every three weeks to 30 patients with a variety of locally advanced or metastatic solid tumors. They escalated the dose from 0.01 mg/kg to as high as 20 mg/kg. The data being presented are the preliminary data from the dose escalation cohorts of the ongoing phase I trial.

No dose-limiting toxicities or grade 4 adverse events have been reported. “We were able to escalate to the top dose without being limited by any serious side effects,” Gordon said.

“From a therapeutic standpoint, we were able to identify a number of patients with a broad range of diseases, including lung cancer, kidney cancer, colon cancer and stomach cancer, who responded to the treatment,” he said.

A second protein, called PD-L2, fits into the same T-cell “outlet” as PD-L1, according to Gordon. MPDL3280A is specific for PD-L1; it does not block PD-L2, which is expressed in noncancerous tissues including the lung, he added.

“One would anticipate, compared with drugs being developed to specifically block the T-cell outlet (PD-1) and, therefore, block the relationship between the outlet and both PD-L1 and PD-L2, that we might see less lung or pulmonary toxicity with MPDL3280A. But we need to conduct larger studies to confirm this.”

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Abstract Number: LB-288

Presenter: Michael S. Gordon, M.D.

Title: A phase 1 study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors

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Background: Programmed Death-Ligand 1 (PD-L1) is the predominant ligand that binds Programmed Death-1 (PD-1), an inhibitory receptor expressed on T cells following T-cell activation. PD-L1 is highly expressed in many human tumors and elevated expression is often associated with a worse prognosis. PD-L1 exerts an immune suppressive signal through binding to PD-1 and B7.1, and tumor expression of PD-L1 can mediate tumor immune evasion. Therefore, inhibition of PD-L1 binding represents an attractive strategy to reinvigorate tumor-specific T-cell immunity. MPDL3280A is a human monoclonal antibody engineered to optimize efficacy and safety through a modification in the Fc region of the antibody. MPDL3280A targets PD-L1, inhibiting interaction with its receptors that include PD-1 and B7.1. In pre-clinical models, inhibition of PD-L1 can lead to durable anti-tumor activity.

Methods: A Phase 1, multicenter, open-label study was conducted to evaluate the safety, pharmacokinetics (PK), and anti-tumor activity of MPDL3280A administered intravenously every 3 weeks (q3w) in pts with locally advanced or metastatic solid tumors. The study includes 3+3 dose-escalation cohorts with a 21-day window to evaluate dose-limiting toxicity (DLT).

Results: As of September 14, 2012, results from the dose escalation include 30 patients (pts) (median age 66 years, range 39-80 years), all PS 0-1, with a median of 2 (range 1-3) prior treatments, received a median of 5.5 doses (range 2-16) of MPDL3280A in 8 dose-escalation cohorts (0.01-20 mg/kg). No DLTs or [Grade (G) \geq 4 adverse events (AEs) attributed to MPDL3280A] have been reported; related G3 AEs were limited to rash in 1 pt. Pneumonitis was not observed in any of the patients in the dose-escalation cohorts. MPDL3280A exposure increased with dose; furthermore, PK was linear at doses \geq 1 mg/kg q3w and consistent with that expected for an IgG1 in humans. RECIST-based responses were observed in a variety of different tumor types with on-going responses in all responding patients.

Conclusions: MPDL3280A was well tolerated with an acceptable safety and efficacy profile in pts with a variety of advanced tumors. PK supports dosing intervals that include q2wk or q3wk administration. An expansion phase in numerous tumor types with biomarker assessments is on-going.